32

Red Blood Cells, Anemia, and Polycythemia

With this chapter we begin discussing the *blood cells* and cells of the *macrophage system* and *lymphatic system.* We first present the functions of red blood cells, which are the most abundant of all the cells of the blood and are necessary for delivery of oxygen to the tissues.

RED BLOOD CELLS (ERYTHROCYTES)

The major function of red blood cells, also known as *erythrocytes,* is to transport *hemoglobin,* which in turn carries oxygen from the lungs to the tissues. In some lower animals, hemoglobin circulates as free protein in the plasma, not enclosed in red blood cells. When it is free in the plasma of the human being, about 3 per cent of it leaks through the capillary membrane into the tissue spaces or through the glomerular membrane of the kidney into the glomerular filtrate each time the blood passes through the capillaries. Therefore, for hemoglobin to remain in the blood stream, it must exist inside red blood cells.

The red blood cells have other functions besides transport of hemoglobin. For instance, they contain a large quantity of *carbonic anhydrase,* which catalyzes the reversible reaction between carbon dioxide and water, increasing the rate of this reaction several thousandfold. The rapidity of this reaction makes it possible for the water of the blood to transport enormous quantities of carbon dioxide from the tissues to the lungs in the form of the bicarbonate ion (HCO_3^-). Also, the hemoglobin in the cells is an excellent *acid-base buffer* (as is true of most proteins), so that the red blood cells are responsible for most of the acid-base buffering power of whole blood.

Shape and Size of Red Blood Cells. Normal red blood cells, shown in Figure 32–3, are biconcave discs having a mean diameter of about 7.8 micrometers and a thickness at the thickest point of 2.5 micrometers and in the center of 1 micrometer or less. The average volume of the red blood cell is 90 to 95 cubic micrometers.

The shapes of red blood cells can change remarkably as the cells squeeze through capillaries. Actually, the red blood cell is a "bag" that can be deformed into almost any shape. Furthermore, because the normal cell has a great excess of cell membrane for the quantity of material inside, deformation does not stretch the membrane greatly and, consequently, does not rupture the cell, as would be the case with many other cells.

Concentration of Red Blood Cells in the Blood. In normal men, the average number of red blood cells per cubic millimeter is 5,200,000 (± 300,000) and in normal women, 4,700,000 (± 300,000). Persons living at high altitudes have greater numbers of red blood cells. This is discussed later.

Quantity of Hemoglobin in the Cells. Red blood cells have the ability to concentrate hemoglobin in the cell fluid up to about 34 g/dl of cells. The concentration does not rise above this value because this is a metabolic limit of the cell's hemoglobin-forming mechanism. Furthermore, in normal people, the percentage of hemoglobin is almost always near the maximum in each cell. However, when hemoglobin formation is deficient, the percentage of hemoglobin in the cells may fall considerably below this value, and the volume of the red cell may also decrease because of diminished hemoglobin to fill the cell.

When the hematocrit (the percentage of the blood that is cells—normally 40 to 45 per cent) and the quantity of hemoglobin in each respective cell are normal, the whole blood of men contains an average of 16 grams of hemoglobin per deciliter and of women, an average of 14 g/dl. As discussed in connection with blood transport of oxygen in Chapter 40, each gram of pure hemoglobin is capable of combining with 1.39 milliliters of oxygen. Therefore, in a normal man, more than 21 milliliters of oxygen can be carried in combination with hemoglobin in each deciliter of blood, and in a normal woman, 19 milliliters of oxygen can be carried.

Production of Red Blood Cells

Areas of the Body That Produce Red Blood Cells. In the early few weeks of embryonic life, primitive, nucleated red blood cells are produced in the *yolk sac.* During the middle trimester of gestation, the *liver* is the main organ for production of red blood cells, although reasonable numbers of red blood cells are also produced in the *spleen* and *lymph nodes.* Then, during the last month or so of gestation and after birth, red blood cells are produced exclusively in the *bone marrow.*

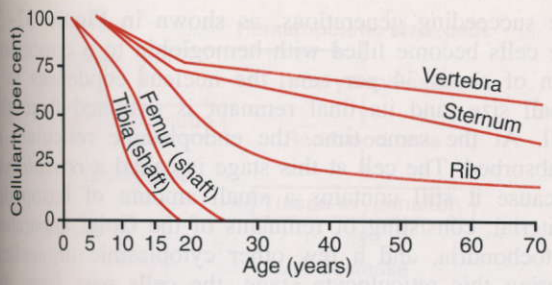


FIGURE 32–1

Relative rates of red blood cell production in the bone marrow of different bones at different ages.

As demonstrated in Figure 32–1, the bone marrow of essentially all bones produces red blood cells until a person is 5 years old; but the marrow of the long bones, except for the proximal portions of the humeri and tibiae, becomes quite fatty and produces no more red blood cells after about age 20 years. Beyond this age, most red cells are produced in the marrow of the membranous bones, such as the vertebrae, sternum, ribs, and ilia. Even in these bones, the marrow becomes less productive as age increases.

Genesis of Blood Cells

Pluripotential Hematopoietic Stem Cells, Growth Inducers, and Differentiation Inducers. In the red cell–producing bone marrow are cells called *pluripotential hematopoietic stem cells,* from which all the cells in the circulating blood are derived. Figure 32–2 shows the successive divisions of the pluripotential cells to form the different peripheral blood cells. As these cells reproduce, continuing throughout life, a small portion of them remains exactly like the original pluripotential cells and is retained in the bone marrow to maintain a supply of these, although their numbers do diminish with age. Most of the reproduced stem cells, however, differentiate to form the other cells shown to the right in Figure 32–2. The early offspring cells still cannot be recognized as different from the pluripotential stem cells, even though they have already become committed to a particular line of cells and are called *committed stem cells.*

The different committed stem cells, when grown in culture, will produce colonies of specific types of blood cells. A committed stem cell that produces erythrocytes is called a *colony-forming unit–erythrocyte,* and the abbreviation CFU-E is used to designate this type of stem cell. Likewise, colony-forming units that form granulocytes and monocytes have the designation CFU-GM, and so forth.

Growth and reproduction of the different stem cells are controlled by multiple proteins called *growth inducers.* Four major growth inducers have been described, each having different characteristics. One of these, *interleukin-3,* promotes growth and reproduction of virtually all the different types of stem cells, whereas the others induce growth of only specific types of committed stem cells.

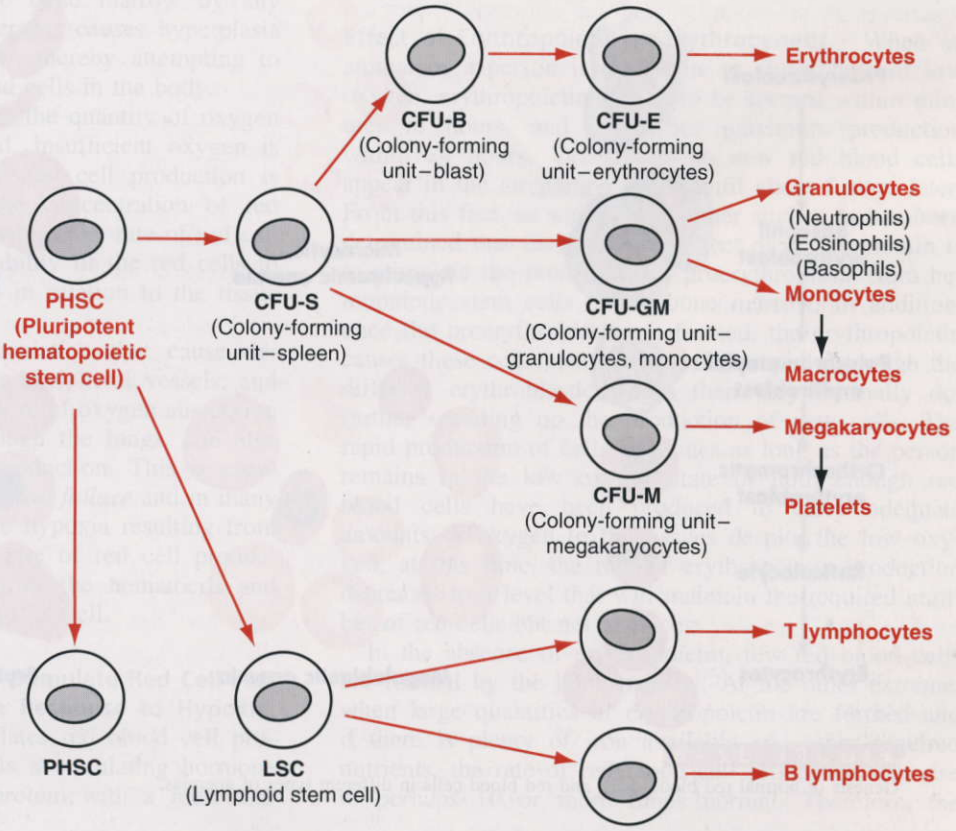


FIGURE 32–2

Formation of the multiple different peripheral blood cells from the original pluripotential hematopoietic stem cell (PHSC) in the bone marrow.

The growth inducers promote growth but not differentiation of the cells. This is the function of still another set of proteins called *differentiation inducers.* Each of these causes one type of stem cell to differentiate one or more steps toward a final type of adult blood cell.

Formation of the growth inducers and differentiation inducers is itself controlled by factors outside the bone marrow. For instance, in the case of red blood cells, exposure of the body to low oxygen for a long time results in growth induction, differentiation, and production of greatly increased numbers of erythrocytes, as we discuss later in the chapter. In the case of some of the white blood cells, infectious diseases cause growth, differentiation, and eventual formation of specific types of white blood cells that are needed to combat the infection.

Stages of Differentiation of Red Blood Cells

The first cell that can be identified as belonging to the red blood cell series is the *proerythroblast,* shown in Figure 32–3. Under appropriate stimulation, large numbers of these cells are formed from the CFU-E stem cells.

Once the proerythroblast has been formed, it divides multiple times, eventually forming many mature red blood cells. The first-generation cells are called *basophil erythroblasts* because they stain with basic dyes; the cell at this time has accumulated very little hemoglobin. In the succeeding generations, as shown in Figure 32–3, the cells become filled with hemoglobin to a concentration of about 34 per cent, the nucleus condenses to a small size, and its final remnant is extruded from the cell. At the same time, the endoplasmic reticulum is reabsorbed. The cell at this stage is called a *reticulocyte* because it still contains a small amount of basophilic material, consisting of remnants of the Golgi apparatus, mitochondria, and a few other cytoplasmic organelles. During this reticulocyte stage, the cells pass from the bone marrow into the blood capillaries by diapedesis (squeezing through the pores of the capillary membrane).

The remaining basophilic material in the reticulocyte normally disappears within 1 to 2 days, and the cell is then the *mature erythrocyte.* Because of the short life of the reticulocytes, their concentration among all the red cells of the blood is normally slightly less than 1 per cent.

Regulation of Red Blood Cell Production—Role of Erythropoietin

The total mass of red blood cells in the circulatory system is regulated within narrow limits, so that an adequate number of red cells is always available to provide sufficient transport of oxygen from the lungs to the tissues, yet the cells do not become so numerous that they impede blood flow. What we know about this

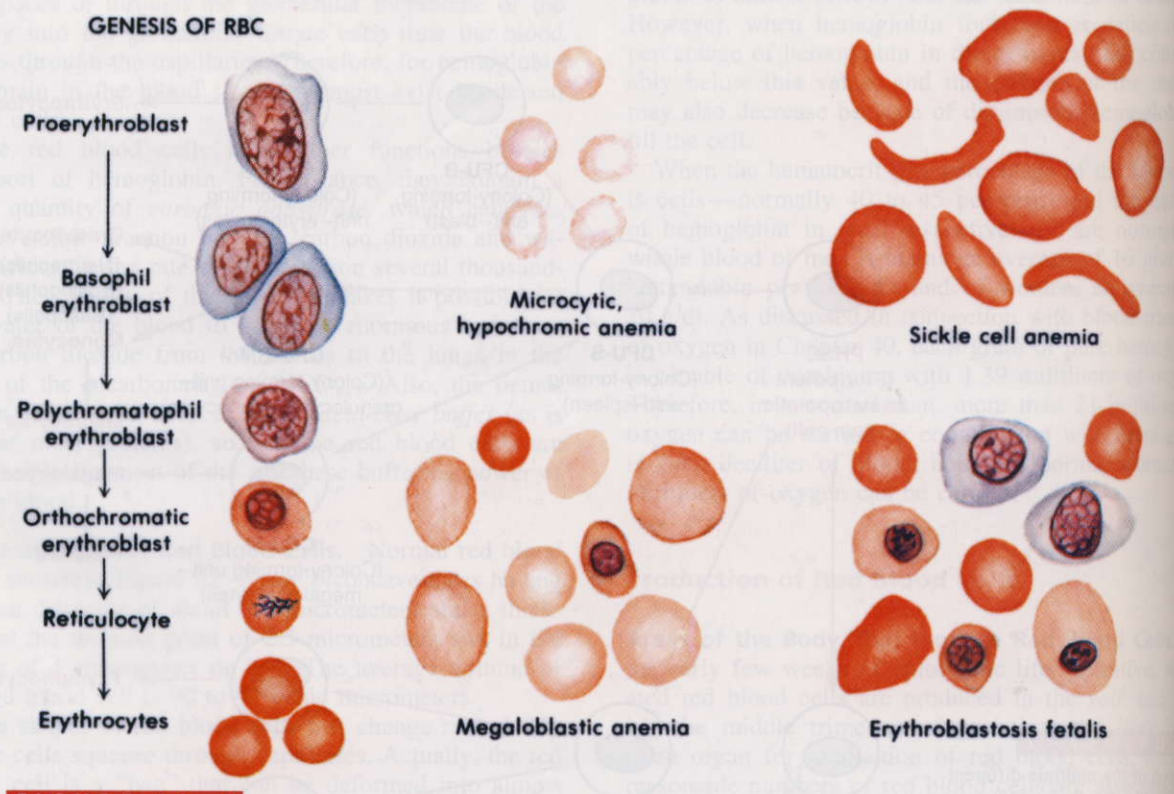


FIGURE 32–3

Genesis of normal red blood cells, and red blood cells in different types of anemias.

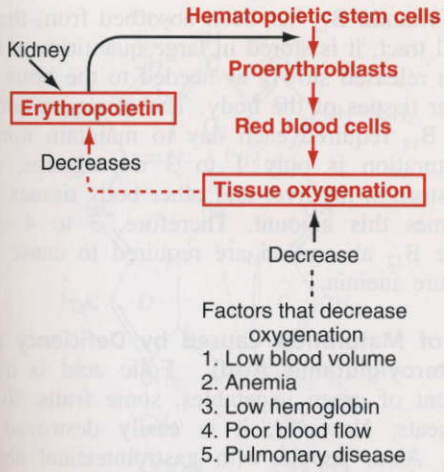


FIGURE 32–4

Function of the erythropoietin mechanism to increase production of red blood cells when various factors decrease tissue oxygenation.

control mechanism is diagrammed in Figure 32–4 and is as follows.

Tissue Oxygenation as the Most Essential Regulator of Red Blood Cell Production. Any condition that causes the quantity of oxygen transported to the tissues to decrease ordinarily increases the rate of red blood cell production. Thus, when a person becomes extremely *anemic* as a result of hemorrhage or any other condition, the bone marrow immediately begins to produce large quantities of red blood cells. Also, destruction of major portions of the bone marrow by any means, especially by x-ray therapy, causes hyperplasia of the remaining bone marrow, thereby attempting to supply the demand for red blood cells in the body.

At very *high altitudes,* where the quantity of oxygen in the air is greatly decreased, insufficient oxygen is transported to the tissues, and red cell production is greatly increased. It is not the concentration of red blood cells in the blood that controls the rate of red cell production but the functional ability of the red cells to transport oxygen to the tissues in relation to the tissue demand for oxygen.

Various diseases of the circulation that cause decreased blood flow through the peripheral vessels, and particularly those that cause failure of oxygen absorption by the blood as it passes through the lungs, can also increase the rate of red cell production. This is especially apparent in prolonged *cardiac failure* and in many *lung diseases* because the tissue hypoxia resulting from these conditions increases the rate of red cell production, with a resultant increase in the hematocrit and usually in the total blood volume as well.

Erythropoietin, Its Function to Stimulate Red Cell Production, and Its Formation in Response to Hypoxia. The principal factor that stimulates red blood cell production in low oxygen states is a circulating hormone called *erythropoietin,* a glycoprotein with a molecular weight of about 34,000. In the absence of erythropoietin, hypoxia has little or no effect in stimulating red blood cell production. Conversely, when the erythropoietin system is functional, hypoxia causes marked increase in erythropoietin production, and the erythropoietin in turn enhances red blood cell production until the hypoxia is relieved.

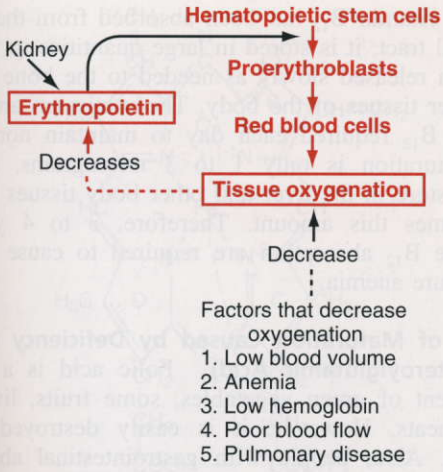
Role of the Kidneys in Formation of Erythropoietin. In the normal person, about 90 per cent of all erythropoietin is formed in the kidneys; the remainder is formed mainly in the liver. It is not known exactly where in the kidneys the erythropoietin is formed. One likely possibility is that the renal tubular epithelial cells secrete the erythropoietin because anemic blood is unable to deliver enough oxygen from the peritubular capillaries to the highly oxygen-consuming tubular cells, thus stimulating erythropoietin production.

At times, hypoxia in other parts of the body but not in the kidneys will also stimulate kidney erythropoietin secretion, which suggests that there might be some nonrenal sensor that sends an additional signal to the kidneys to produce this hormone. In particular, both norepinephrine and epinephrine and several of the prostaglandins stimulate erythropoietin production.

When both kidneys are removed from a person or when the kidneys are destroyed by renal disease, the person invariably becomes very anemic because the 10 per cent of the normal erythropoietin formed in other tissues (mainly in the liver) is sufficient to cause only one third to one half as much red blood cell formation as needed by the body.

Effect of Erythropoietin in Erythrogenesis. When an animal or a person is placed in an atmosphere of low oxygen, erythropoietin begins to be formed within minutes to hours, and it reaches maximum production within 24 hours. Yet almost no new red blood cells appear in the circulating blood until about 5 days later. From this fact, as well as still other studies, it has been determined that the important effect of erythropoietin is to stimulate the production of proerythroblasts from hemopoietic stem cells in the bone marrow. In addition, once the proerythroblasts are formed, the erythropoietin causes these cells also to pass more rapidly through the different erythroblastic stages than they normally do, further speeding up the production of new cells. The rapid production of cells continues as long as the person remains in the low oxygen state or until enough red blood cells have been produced to carry adequate amounts of oxygen to the tissues despite the low oxygen; at this time, the rate of erythropoietin production decreases to a level that will maintain the required number of red cells but not an excess.

In the absence of erythropoietin, few red blood cells are formed by the bone marrow. At the other extreme, when large quantities of erythropoietin are formed and if there is plenty of iron available and other required nutrients, the rate of red blood cell production can rise to perhaps 10 or more times normal. Therefore, the



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erythropoietin control mechanism for red blood cell production is a powerful one.

Maturation of Red Blood Cells—Requirement for Vitamin B_{12} (Cyanocobalamin) and Folic Acid

Because of the continuing need to replenish red blood cells, the erythropoietic cells of the bone marrow are among the most rapidly growing and reproducing cells of the entire body. Therefore, as would be expected, their maturation and rate of production are affected greatly by a person's nutritional status.

Especially important for final maturation of the red blood cells are two vitamins, *vitamin B_{12}* and *folic acid.* Both of these are essential for the synthesis of DNA because each in a different way is required for the formation of thymidine triphosphate, one of the essential building blocks of DNA. Therefore, lack of either vitamin B_{12} or folic acid causes diminished DNA and, consequently, failure of nuclear maturation and division. Furthermore, the erythroblastic cells of the bone marrow, in addition to failing to proliferate rapidly, produce mainly larger than normal red cells called *macrocytes,* and the cell has a flimsy membrane and is often irregular, large, and oval instead of the usual biconcave disc. These poorly formed cells, after entering the circulating blood, are capable of carrying oxygen normally, but their fragility causes them to have a short life, one-half to one-third normal. Therefore, it is said that either vitamin B_{12} or folic acid deficiency causes *maturation failure* in the process of erythropoiesis.

The cause of the abnormal cells seems to be as follows: The inability of the cells to synthesize adequate quantities of DNA leads to slow reproduction of the cells. Because of abnormalities of the DNA, the structural components of the cell membrane and cytoskeleton are also malformed, which leads to the abnormal cell shapes and especially the greatly increased cell membrane fragility.

Maturation Failure Caused by Poor Absorption of Vitamin B_{12}—Pernicious Anemia. A common cause of maturation failure is failure to absorb vitamin B_{12} from the gastrointestinal tract. This often occurs in the disease *pernicious anemia,* in which the basic abnormality is an *atrophic gastric mucosa* that fails to secrete normal gastric secretions. The parietal cells of the gastric glands secrete a glycoprotein called *intrinsic factor,* which combines with vitamin B_{12} in food and makes the B_{12} available for absorption by the gut. It does this in the following way: (1) The intrinsic factor binds tightly with the vitamin B_{12}. In this bound state, the B_{12} is protected from digestion by the gastrointestinal enzymes. (2) Still in the bound state, the intrinsic factor binds to specific receptor sites on the brush border membranes of the mucosal cells in the ileum. (3) Vitamin B_{12} is transported into the blood during the next few hours by the process of pinocytosis, carrying the intrinsic factor and the vitamin together through the membrane.

Lack of intrinsic factor, therefore, causes loss of much of the vitamin because of both digestive enzyme action in the gut and failure of its absorption.

Once vitamin B_{12} has been absorbed from the gastrointestinal tract, it is stored in large quantities in the liver and then released slowly as needed to the bone marrow and other tissues of the body. The minimum amount of vitamin B_{12} required each day to maintain normal red cell maturation is only 1 to 3 micrograms, and the normal store in the liver and other body tissues is about 1000 times this amount. Therefore, 3 to 4 years of defective B_{12} absorption are required to cause maturation failure anemia.

Failure of Maturation Caused by Deficiency of Folic Acid (Pteroylglutamic Acid). Folic acid is a normal constituent of green vegetables, some fruits, liver, and other meats. However, it is easily destroyed during cooking. Also, people with gastrointestinal absorption abnormalities, such as the frequently occurring small intestinal disease called *sprue,* often have serious difficulty in absorbing both folic acid and vitamin B_{12}. Therefore, in many instances of maturation failure, the cause is deficiency of intestinal absorption of both folic acid and vitamin B_{12}.

Formation of Hemoglobin

Synthesis of hemoglobin begins in the proerythroblasts and continues even into the reticulocyte stage because when the reticulocytes leave the bone marrow and pass into the blood stream, they continue to form minute quantities of hemoglobin for another day or so.

Figure 32–5 shows the basic chemical steps in the formation of hemoglobin. First, succinyl-CoA, formed in the Krebs cycle as explained in Chapter 67, binds with glycine to form a pyrrole molecule. In turn, four pyrroles combine to form protoporphyrin IX, which then combines with iron to form the *heme* molecule. Finally, each heme molecule combines with a long polypeptide chain, called a *globin,* synthesized by the ribosomes, forming a subunit of hemoglobin called a *hemoglobin chain* (Figure 32–6). Each of these chains has a molecular weight of about 16,000; four of them in turn bind together loosely to form the whole hemoglobin molecule.

There are several slight variations in different subunit hemoglobin chains, depending on the amino acid composition of the polypeptide portion. The different types

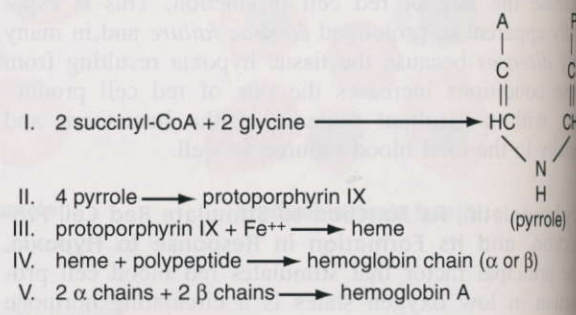

FIGURE 32–5

Formation of hemoglobin.

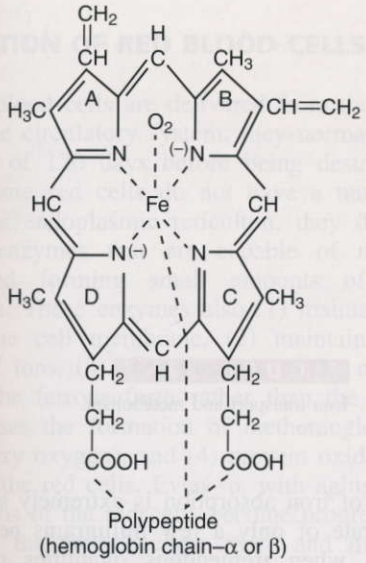

FIGURE 32–6

Basic structure of the hemoglobin molecule, showing one of the four heme chains that bind together to form the hemoglobin molecule.

of chains are designated *alpha chains, beta chains, gamma chains,* and *delta chains.* The most common form of hemoglobin in the adult human being, *hemoglobin A,* is a combination of *two alpha chains* and *two beta chains.* Hemoglobin A has a molecular weight of 64,458.

Because each hemoglobin chain has a heme prosthetic group containing an atom of iron, and because there are four hemoglobin chains in each hemoglobin molecule, one finds four iron atoms in each hemoglobin molecule; each of these can bind with one molecule of oxygen, making a total of four molecules of oxygen (or eight oxygen atoms) that can be transported by each hemoglobin molecule.

The nature of the hemoglobin chains determines the binding affinity of the hemoglobin for oxygen. Abnormalities of the chains can alter the physical characteristics of the hemoglobin molecule as well. For instance, in *sickle cell anemia,* the amino acid *valine* is substituted for *glutamic acid* at one point in each of the two beta chains. When this type of hemoglobin is exposed to low oxygen, it forms elongated crystals inside the red blood cells that are sometimes 15 micrometers in length. These make it almost impossible for the cells to pass through many small capillaries, and the spiked ends of the crystals are likely to rupture the cell membranes, thus leading to sickle cell anemia.

Combination of Hemoglobin with Oxygen. The most important feature of the hemoglobin molecule is its ability to combine loosely and reversibly with oxygen. This ability is discussed in detail in Chapter 40 in relation to respiration because the primary function of hemoglobin in the body is its ability to combine with oxygen in the lungs and then to release this oxygen readily in the tissue capillaries where the gaseous tension of oxygen is much lower than in the lungs.

Oxygen *does not* combine with the two positive bonds of the iron in the hemoglobin molecule. Instead, it binds loosely with one of the so-called coordination bonds of the iron atom. This is an extremely loose bond so that the combination is easily reversible. Furthermore, the oxygen does not become ionic oxygen but is carried as molecular oxygen, composed of two oxygen atoms, to the tissues, where, because of the loose, readily reversible combination, it is released into the tissue fluids still in the form of molecular oxygen, rather than ionic oxygen.

Iron Metabolism

Because iron is important for the formation of hemoglobin, myoglobin, and other substances such as the cytochromes, cytochrome oxidase, peroxidase, and catalase, it is essential to understand the means by which iron is utilized in the body.

The total quantity of iron in the body averages 4 to 5 grams, about 65 per cent of which is in the form of hemoglobin. About 4 per cent is in the form of myoglobin, 1 per cent is in the form of the various heme compounds that promote intracellular oxidation, 0.1 per cent is combined with the protein transferrin in the blood plasma, and 15 to 30 per cent is stored mainly in the reticuloendothelial system and liver parenchymal cells, principally in the form of ferritin.

Transport and Storage of Iron. Transport, storage, and metabolism of iron in the body are diagrammed in Figure 32–7 and may be explained as follows: When iron is absorbed from the small intestine, it immediately combines in the blood plasma with a beta globulin, *apotransferrin,* to form *transferrin,* which is then transported in the plasma. The iron is loosely bound in the transferrin and, consequently, can be released to any of the tissue cells at any point in the body. Excess iron in the blood is deposited in all cells of the body, but *especially* in the liver hepatocytes and less in the reticuloendothelial cells of the bone marrow. In the receiving cell cytoplasm, the iron combines mainly with a protein, *apoferritin,* to form *ferritin.* Apoferritin has a molecular weight of about 460,000, and varying quantities of iron can combine in clusters of iron radicals with this large molecule; therefore, ferritin may contain only a small amount of iron or a large amount. This iron stored as ferritin is called *storage iron.*

Smaller quantities of the iron in the storage pool are stored in an extremely insoluble form called *hemosiderin.* This is especially true when the total quantity of iron in the body is more than the apoferritin storage pool can accommodate. Hemosiderin forms especially large clusters in the cells and, consequently, can be stained and observed microscopically as large particles in tissue slices. Ferritin can also be stained, but the ferritin particles are so small and dispersed that they usually can be seen only with the electron microscope.

When the quantity of iron in the plasma falls very low, iron is removed from ferritin quite easily but from

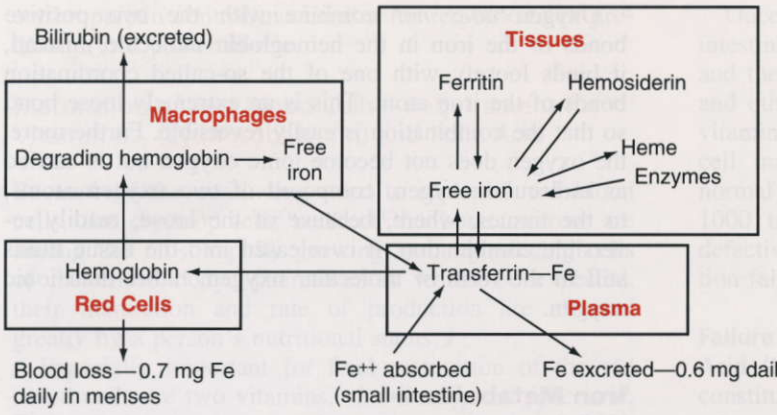

FIGURE 32–7
Iron transport and metabolism.

hemosiderin much less easily. The iron is then transported again in the form of transferrin in the plasma to the portions of the body where it is needed.

A unique characteristic of the transferrin molecule is that it binds strongly with receptors in the cell membranes of erythroblasts in the bone marrow. Then, along with its bound iron, it is ingested into the erythroblasts by endocytosis. There the transferrin delivers the iron directly to the mitochondria, where heme is synthesized. In people who do not have adequate quantities of transferrin in their blood, failure to transport iron to the erythroblasts in this manner can cause severe hypochromic anemia—that is, red cells that contain much less hemoglobin than normal.

When red blood cells have lived their life span and are destroyed, the hemoglobin released from the cells is ingested by the cells of the monocyte-macrophage system. There free iron is liberated, and it is then mainly stored in the ferritin pool or reused for formation of new hemoglobin.

Daily Loss of Iron. A man excretes about 0.6 milligram of iron each day, mainly into the feces. Additional quantities of iron are lost whenever bleeding occurs. For a woman, the menstrual loss of blood brings the iron loss to an average value of about 1.3 mg/day.

Absorption of Iron from the Gastrointestinal Tract

Iron is absorbed from all parts of the small intestine, mostly by the following mechanism. The liver secretes moderate amounts of *apotransferrin* into the bile that flows through the bile duct into the duodenum. In the small intestine, the apotransferrin binds with free iron and also with certain iron compounds such as hemoglobin and myoglobin from meat, two of the most important sources of iron in the diet. This combination is called *transferrin.* It in turn is attracted to and binds with receptors in the membranes of the intestinal epithelial cells. Then, by pinocytosis, the transferrin molecule, carrying with it its iron store, is absorbed into the epithelial cells and later is released into the blood capillaries beneath these cells in the form of *plasma transferrin.*

The rate of iron absorption is extremely slow, with a maximum rate of only a few milligrams per day. This means that when tremendous quantities of iron are present in the food, only small proportions of this can be absorbed.

Regulation of Total Body Iron by Controlling Rate of Absorption. When the body has become saturated with iron so that essentially all the apoferritin in the iron storage areas is already combined with iron, the rate of absorption of iron from the intestinal tract becomes greatly decreased. Conversely, when the iron stores have been depleted of iron, the rate of absorption can become accelerated probably to five or more times as great as when the iron stores are normally saturated. Thus, the total body iron is regulated to a great extent by altering the rate of absorption.

Feedback Mechanisms for Regulating Iron Absorption. Two mechanisms that play at least some role in regulating iron absorption are the following: (1) When essentially all the apoferritin in the body has become saturated with iron, it becomes difficult for transferrin to release iron to the tissues. As a consequence, the transferrin, which is normally only one-third saturated with iron, now becomes almost fully bound with iron, so that the transferrin accepts almost no new iron from the mucosal cells of the intestines. Then, as a final stage of this process, the buildup of excess iron in the mucosal cells themselves depresses active absorption of iron from the intestinal lumen. (2) When the body already has excess stores of iron, the liver decreases its rate of formation of apotransferrin, thus reducing the concentration of this iron-transporting molecule in the plasma and the bile. Therefore, less iron is absorbed by the intestinal apotransferrin mechanism, and less iron can be transported away from the intestinal epithelial cells in the plasma by plasma transferrin.

Yet, despite these feedback control mechanisms for regulating iron absorption, when a person eats extremely large amounts of iron compounds, excess iron does enter the blood and can lead to massive deposition of hemosiderin in the reticuloendothelial cells throughout the body. At times, this can be very damaging.

DESTRUCTION OF RED BLOOD CELLS

When red blood cells are delivered from the bone marrow into the circulatory system, they normally circulate an average of 120 days before being destroyed. Even though mature red cells do not have a nucleus, mitochondria, or endoplasmic reticulum, they do have cytoplasmic enzymes that are capable of metabolizing glucose and forming small amounts of adenosine triphosphate. These enzymes also (1) maintain the pliability of the cell membrane, (2) maintain membrane transport of ions, (3) keep the iron of the cells' hemoglobin in the ferrous form rather than the ferric form (which causes the formation of methemoglobin, which will not carry oxygen), and (4) prevent oxidation of the proteins in the red cells. Even so, with aging, the metabolic systems of the red cells become progressively less active, and the cells become more and more fragile, presumably because their life processes wear out.

Once the red cell membrane becomes fragile, the cell ruptures during passage through some tight spot of the circulation. Many of the red cells self-destruct in the spleen, where they squeeze through the red pulp of the spleen. Here the spaces between the structural trabeculae of the red pulp, through which most of the cells must pass, are only 3 micrometers wide, in comparison with the 8-micrometer diameter of the red cell. When the spleen is removed, the number of abnormal red cells and old cells circulating in the blood increases considerably.

Destruction of Hemoglobin. When red blood cells burst and release their hemoglobin, the hemoglobin is phagocytized almost immediately by macrophages in many parts of the body, but especially by the Kupffer cells of the liver and macrophages of the spleen and bone marrow. During the next few hours to days, the macrophages release the iron from the hemoglobin and pass it back into the blood to be carried by transferrin either to the bone marrow for production of new red blood cells or to the liver and other tissues for storage in the form of ferritin. The porphyrin portion of the hemoglobin molecule is converted by the macrophages, through a series of stages, into the bile pigment *bilirubin,* which is released into the blood and later secreted by the liver into the bile; this is discussed in relation to liver function in Chapter 70.

THE ANEMIAS

Anemia means a deficiency of hemoglobin, which can be caused by either too few red blood cells or too little hemoglobin in the cells. Some types of anemia and their physiologic causes are the following.

Blood Loss Anemia. After rapid hemorrhage, the body replaces the fluid portion of the plasma in 1 to 3 days, but this leaves a low concentration of red blood cells. If a second hemorrhage does not occur, the red blood cell concentration usually returns to normal within 3 to 6 weeks.

In chronic blood loss, a person frequently cannot absorb enough iron from the intestines to form hemoglobin as rapidly as it is lost. Red cells are then produced that are much smaller than normal and have too little hemoglobin inside them, giving rise to *microcytic, hypochromic anemia,* which is shown in Figure 32–3.

Aplastic Anemia. *Bone marrow aplasia* means lack of a functioning bone marrow. For instance, a person exposed to gamma ray radiation from a nuclear bomb blast is likely to sustain complete destruction of bone marrow, followed in a few weeks by lethal anemia. Likewise, excessive x-ray treatment, certain industrial chemicals, and even drugs to which the person might be sensitive can cause the same effect.

Megaloblastic Anemia. From the earlier discussion of vitamin B_{12}, folic acid, and intrinsic factor from the stomach mucosa, one can readily understand that loss of any one of these factors can lead to slow reproduction of the erythroblasts in the bone marrow. As a result, these grow too large, with odd shapes, and are called *megaloblasts.* Thus, atrophy of the stomach mucosa, as occurs in *pernicious anemia,* or loss of the entire stomach as the result of surgical total gastrectomy can lead to megaloblastic anemia. Also, patients who have intestinal sprue, in which folic acid, vitamin B_{12}, and other vitamin B compounds are poorly absorbed, often develop megaloblastic anemia. Because the erythroblasts cannot proliferate rapidly enough to form normal numbers of red blood cells, the cells that are formed are mostly oversized, have bizarre shapes, and have fragile membranes. These cells rupture easily, leaving the person in dire need of an adequate number of red cells.

Hemolytic Anemia. Different abnormalities of the red blood cells, many of which are hereditarily acquired, make the cells fragile, so that they rupture easily as they go through the capillaries, especially through the spleen. Even though the number of red blood cells formed is normal, or even much greater than normal in some hemolytic diseases, the red cell life span is so short that cells are destroyed much faster than they can be formed, and serious anemia results. Some of these types of anemia are the following.

In *hereditary spherocytosis,* the red cells are very small and *spherical,* rather than being biconcave discs. These cells cannot withstand compression forces because they do not have the normal loose, baglike cell membrane structure of the biconcave discs. On passing through the splenic pulp and some other tissues, they are easily ruptured by even slight compression.

In *sickle cell anemia,* which is present in 0.3 to 1.0 per cent of West African and American blacks, the cells contain an abnormal type of hemoglobin called *hemoglobin S,* caused by abnormal beta chains of the hemo-

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globin molecule, as explained earlier in the chapter. When this hemoglobin is exposed to low concentrations of oxygen, it precipitates into long crystals inside the red blood cell. These crystals elongate the cell and give it the appearance of being a sickle, rather than a biconcave disc. The precipitated hemoglobin also damages the cell membrane, so that the cells become highly fragile, leading to serious anemia. Such patients frequently go into a vicious circle called a sickle cell disease "crisis," in which low oxygen tension in the tissues causes sickling, which causes ruptured red cells, this in turn causing still further decrease in oxygen tension and still more sickling and red cell destruction. Once the process starts, it progresses rapidly, leading to serious decrease in red blood cell mass within a few hours and, often, death.

In *erythroblastosis fetalis,* Rh-positive red blood cells in the fetus are attacked by antibodies from an Rh-negative mother. These antibodies make the Rh-positive cells fragile, leading to rapid rupture and causing the child to be born with serious anemia. This is discussed in Chapter 35 in relation to the Rh factor of blood. The extremely rapid formation of new red cells to make up for the destroyed cells in erythroblastosis fetalis causes a large number of early *blast* forms of red cells to be released into the blood.

EFFECTS OF ANEMIA ON THE CIRCULATORY SYSTEM

The viscosity of the blood, which was discussed in Chapter 14, depends almost entirely on the blood concentration of red blood cells. In severe anemia, the blood viscosity may fall to as low as 1.5 times that of water rather than the normal value of about 3. This decreases the resistance to blood flow in the peripheral blood vessels so that far greater than normal quantities of blood then flow through the tissues and return to the heart. Moreover, hypoxia resulting from diminished transport of oxygen by the blood causes the peripheral tissue vessels to dilate, allowing still further increase in return of blood to the heart, increasing the cardiac output to a still higher level, sometimes to levels three to four times normal. Thus, one of the major effects of anemia is greatly *increased pumping workload on the heart.*

The increased cardiac output in anemia partially offsets the reduced oxygen-carrying effect of anemia because even though each unit quantity of blood carries only small quantities of oxygen, the rate of blood flow may be increased enough so that almost normal quantities of oxygen are actually delivered to the tissues. However, when this same person with anemia begins to exercise, the heart is not capable of pumping much greater quantities of blood than it is already pumping. Consequently, during exercise, which greatly increases tissue demand for oxygen, extreme tissue hypoxia results, and acute cardiac failure ensues.

POLYCYTHEMIA

Secondary Polycythemia. Whenever the tissues become hypoxic because of too little oxygen in the atmosphere, such as at high altitudes, or because of failure of delivery of oxygen to the tissues, as occurs in cardiac failure, the blood-forming organs automatically produce large quantities of extra red blood cells. This condition is called *secondary polycythemia,* and the red cell count commonly rises to 6 to 7 million/mm^3, about 30 per cent above normal.

A common type of secondary polycythemia, called *physiologic polycythemia,* occurs in natives who live at altitudes of 14,000 to 17,000 feet. The blood count is generally 6 to 7 million/mm^3; this is associated with the ability of these people to perform high levels of continuous work even in a rarefied atmosphere.

Polycythemia Vera (Erythremia). In addition to those people who have physiologic polycythemia, others have a pathological condition known as *polycythemia vera,* in which the red blood cell count may be 7 to 8 million/mm^3 and the hematocrit 60 to 70 per cent. Polycythemia vera is caused by a genetic aberration that occurs in the hemocytoblastic cell line that produces the blood cells. The blast cells no longer stop producing red cells when too many cells are already present. This causes excess production of red blood cells in the same manner that a tumor of a breast causes excess production of a specific type of breast cell. It usually causes excess production of white blood cells and platelets as well.

In polycythemia vera, not only does the hematocrit increase, but the total blood volume also increases, on some occasions to almost twice the normal level. As a result, the entire vascular system becomes intensely engorged. In addition, many of the capillaries become plugged by the viscous blood because the viscosity of the blood in polycythemia vera sometimes increases from the normal of 3 times the viscosity of water to 10 times that of water.

Effect of Polycythemia on the Circulatory System

Because of the greatly increased viscosity of the blood in polycythemia, the flow of blood through the vessels is often very sluggish. In accordance with the factors that regulate the return of blood to the heart, as discussed in Chapter 20, increasing the viscosity tends to *decrease* the rate of venous return to the heart. Conversely, the blood volume is greatly increased in polycythemia, which tends to *increase* the venous return. Actually, the cardiac output in polycythemia is not far from normal because these two factors more or less neutralize each other.

The arterial pressure is also normal in most people with polycythemia, though in about one third of them the arterial pressure is elevated. This means that the

blood pressure-regulating mechanisms can usually offset the tendency for increased blood viscosity to increase peripheral resistance and, thereby, increase arterial pressure. Beyond certain limits, however, these regulations fail.

The color of the skin depends to a great extent on the quantity of blood in the skin subpapillary venous plexus. In polycythemia vera, the quantity of blood in this plexus is greatly increased. Furthermore, because the blood passes sluggishly through the skin capillaries before entering the venous plexus, a larger than normal quantity of hemoglobin is deoxygenated. The blue color of all this deoxygenated hemoglobin masks the red color of the oxygenated hemoglobin. Therefore, a person with polycythemia vera ordinarily has a ruddy complexion with a bluish (cyanotic) tint to the skin.

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